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Kinetics of Drug Delivery to the Arterial Wall Via Polyurethane-Coated Removable Nitinol Stent: Comparative Study of Two Drugs

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Polymer-coated removable stents were used to deliver ^{14}C-labeled etretinate and ^{3}H-labeled forskolin to the vessel wall in 31 New Zealand White rabbits to study their kinetics. Stents loaded with etretinate (n = 8) and forskolin (n = 14) were implanted in the rabbit carotid arteries, and the animals were euthanized at different time intervals. Drug levels were measured in the media and adventitia of the stented segment, in distant tissues, and in blood. In four rabbits, forskolin-loaded stents were percutaneously retrieved 2 hr after implantation in the carotid artery, and the tissue and blood levels were determined 2 and 24 hr after retrieval. In seven rabbits etretinate-loaded stents were retrieved 72 hr after implantation in abdominal aorta, and drug levels were measured in the tissues and blood immediately after and at 1 and 4 days after retrieval.

Levels of etretinate in the vessel wall peaked at 24 hr (250 ng/mg) and remained high up to 72 hr (185 ng/mg) after stent placement. Levels of forskolin peaked within 2 hr of stent placement (135 ng/mg) and rapidly declined to 4.9 ng/mg at 24 hr with the stent in situ. About 50% (1.4 mg) of the original etretinate remained in the stent at 72 hr compared to about 5% (0.08 mg) of forskolin at 24 hr. Ratio of peak drug levels in the vessel wall to those in the blood was 6,000 for etretinate and 780 for forskolin. After stent removal at 72 hr, levels of etretinate in the aortic wall declined from 74 ng/mg to 29 ng/mg at 1 day and to 14 ng/mg at 4 days. Levels of forskolin declined rapidly within 2 hr of stent removal from 134 ng/mg to 1.2 ng/mg and further to 0.12 ng/mg within 24 hr. Polymer-coated stents could be used for local drug delivery to the vessel wall. Kinetics of delivery and washout vary between drugs.

Key words: angioplasty, local drug delivery, restenosis

INTRODUCTION

Despite advances in interventional technology, restenosis occurs in 25–50% of patients following coronary angioplasty [1,2]. There are two principal mechanisms underlying the restenotic process: first, geometric remodeling of the lesion which results in luminal renarrowing without increase in the mass of the residual atherosclerotic plaque [3], and second, an increase in the mass of the plaque tissue due to intimal hyperplasia, matrix synthesis, and incorporation of mural or luminal thrombus [4,5]. The relative contribution of each of these mechanisms varies, and the interaction between them is not completely understood [5]. It is logical, however, that the effective management for prevention of restenosis should address both of these mechanisms.

Several clinical trials of systemically administered drugs, previously demonstrated to be effective in animal models of restenosis, have yielded negative results [1,2], possibly as a result of insufficient concentration of drug in the target tissues. Local delivery of high concentrations of antiproliferative and antithrombotic drugs has the potential to achieve much higher arterial drug levels than those with systemic administration. Two randomized trials comparing Palmaz-Schatz coronary stent placement with balloon angioplasty for selected de novo lesions in native coronary arteries have shown significant reductions in restenosis rates, possibly by achieving greater initial gain and minimizing late geometric remod-

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eling [6,7]. The combination of stent placement with local drug delivery, therefore, may have a value as a further therapeutic approach to restenosis.

Our group has recently reported on the development of the heat-activated removable stent [8,9], which may be useful both as a temporary stent and as a drug delivery device. The purpose of this study was twofold: first, to test a polymer-coated removable stent system for local delivery of two lipid soluble drugs—etretinate and forskolin as two model agents with antiproliferative and antiplatelet properties, respectively, and second, to compare these two drugs with respect to kinetics of their delivery to the arterial wall with the stent in place and their tissue washout rates after removal of the stent.

MATERIALS AND METHODS

The Stent

Although the polymer coating is potentially usable with any stent, all our studies were performed with a heat-activated removable temporary stent (HARTS, Advanced Coronary Technologies, Menlo Park, CA). This stent is made of nitinol, an alloy with unique shape memory properties [8,9]. The stent is percutaneously implanted into the vessel wall by balloon expansion and is subsequently recovered to its predeployment dimensions by transiently heating it to its preselected thermoelastic transition temperature of 55°C [8,9]. This property permits percutaneous removal of the stent, which has been accomplished up to 1 week after deployment in canine coronary arteries [8]. Our studies have been performed on a prototype of this stent constructed from the nitinol wire segments of 0.009 inch diameter.

Polymer Coating and Drug Loading

We used a commercially available biomedical grade polyurethane (Tecoflex, Thermetics, Woburn MA). Tecoflex is a biocompatible, flexible, and an elastic membrane–forming polymer [10]. Stents were spray coated with about a 50-μm-thick layer of tecoflex (about 15 mg tecoflex per stent), using a 2–4% solution of tecoflex in tetrahydrofuran. This polymer coating swells up in a specific solvent mixture without dissolving in it. A solution of ^{3}H-labeled forskolin (20 mg/ml forskolin with specific activity of 25 μCi/mg) and ^{14}C-labeled etretinate (20 mg/ml etretinate with specific activity of 40 μCi/mg) was prepared in this solvent mixture. The polymer-coated stents were incubated in this solution for 6 min at 29°C. Polymer coating imbibed some of the solution during this process by swelling like a sponge. These stents were then dried in a partial vacuum at 40°C for 24 hr to let the solvent evaporate and membrane shrink thus, leaving the drugs trapped in the interstices of the polymer. The amount of drug loaded on a stent depends on the weight of the polymer, the degree of polymer swelling, and the concentration of the drug in the solution. As tecoflex optimally swells in a specific mixture of organic solvents, the nature and amount of drugs that can be loaded on the stent is limited by their solubility in this mixture. We could incorporate about 1.5 mg of forskolin and 2.8 mg of etretinate on a stent by this method.

Drugs

To study the kinetics of drug delivery, we used two lipid soluble compounds: forskolin and etretinate. Forskolin (Calbiochem, La Jolla, CA), a diterpene (mol wt 410), isolated from the roots of the Indian plant *Coleus forskohlii*, is a direct adenylate cyclase activator [11–13]. Forskolin thus acts as a potent antiplatelet, vasodilator, and positive inotropic agent, and these activities have been directly correlated with a rise in cyclic adenosine monophosphate levels [11–13]. Etretinate (Hoffman-LaRoche, Nutley, NJ) is a long-acting retinoid (vitamin A analogue) with an aromatic ring and a long side chain (mol wt 355). Retinoids are known to modify cell proliferation in many cutaneous and hematological disorders by preventing the phenotypic change from quiescent or slowly proliferating cells to rapid uncontrolled proliferation [14]. The retinoids also increase apolipoprotein A levels, thus favorably altering the lipoprotein melieu [15]. Some retinoids (not etretinate) also increase tissue plasminogen activator (tPA) levels and are thus profibrinolytic [16]. ^{3}H-Labeled forskolin was obtained from New England Nuclear (Boston, MA), and ^{14}C-labeled etretinate was from Hoffman-Laroche (Nutley, NJ).

Animal Procedures

Studies were performed on New Zealand White (NZW) rabbits weighing 3.5–4.0 kg. The animals were kept in the institutional core facility with appropriate veterinary care. All animal experiments conformed with the guiding principles of the American Physiological Society and were approved by the Institutional Animal Care and Use Committee.

Study of Drug Delivery Kinetics With Stents In Situ

NZW rabbits (n = 19) were anesthetized with intravenous xylazine and ketamine. After femoral cutdown, a 6F introducer sheath was placed in the left femoral artery. Polymer-coated stents loaded with radiolabeled for-

skolin or etretinate were mounted on a 3.0-mm-diameter, 20-mm-long percutaneous transluminal coronary angioplasty (PTCA) balloon catheter. The assembly was introduced through the femoral artery sheath and positioned into the right carotid artery over a 0.014" floppy guidewire. The stent was then deployed in the carotid artery by inflating the balloon for 1 min at 6 atm pressure. The balloon catheter and guidewire were withdrawn after deflation of the balloon. The animals were then euthanized by an intravenous injection of potassium chloride at varying time intervals after deployment of the stents.

For the etretinate study, animals (n = 8) were euthanized 4, 24, 48, and 72 hr after stent placement (two animals at each time point). In the forskolin study, euthanasia was performed at 2 hr (n = 2), 4 hr (n = 6), and 24 hr (n = 3) after stent placement. Because >95% of forskolin cleared from the stent at 24 hr, 48- and 72-hr time points were omitted for the forskolin group and a 2-hr time point was added. Tissue and blood samples were taken for measuring drug levels.

Drug Washout Study After Stent Removal

Stents loaded with ^{3}H-labeled forskolin were implanted in the carotid arteries of four NZW rabbits. The stents were retrieved after 2 hr, and the animals were euthanized at 2 hr (n = 2) or at 24 hr (n = 2) after removal of the stent. Drug washout curves were drawn by taking three time points: 1) tissue levels 2 hr after implantation of the stent as time 0, 2) Tissue levels 2 hr after removal of the stent, and 3) tissue levels 24 hr after removal of the stent. For studying the etretinate washout, stents loaded with ^{14}C-labeled etretinate were implanted in the abdominal aorta (for ease of stent retrieval) in seven rabbits, through a 6F arterial sheath, introduced via femoral artery cutdown. The stents were retrieved after 72 hr, and the animals were euthanized 1) immediately after (n = 3) 2) 1 day after (n = 2), and 3) 4 days after (n = 2) removal of the stent. Drug washout curves were drawn using these three time points. Timing of stent retrieval for this study (2 hr for forskolin and 72 hr for etretinate) was based on tissue levels of the drug achieved with the stent in place. With the stent in place, forskolin levels declined rapidly after 2 hr, whereas those of etretinate remained high until 72 hr. Tissue and blood samples were taken for measuring drug levels. To recover stents, a 3F catheter with multiple side holes was passed over a guidewire until it was co-axial within the stent. A 5-ml bolus of heated normal saline (65°C) was injected through the retrieval catheter resulting in immediate collapse of the stent to its predeployment diameter, tightly gripping the catheter. The collapsed stent, the retrieval catheter, and the guidewire were then removed en bloc through the femoral arterial sheath.

Measurements of Tissue Drug Levels

At euthanasia the following tissue samples (6–30 mg) were obtained in all animals: a) adventitia and media of the 1) stented arterial segments, 2) arterial segment proximal to the stent, 3) arterial segments 1 cm and 2 cm distal to the stent, and 4) nonstented carotid artery; b) fat and muscle adjacent to the artery; c) liver and kidney; and d) blood. Adventitia was surgically stripped from the vessel media. Blood samples were also obtained before implantation of the stent and 1/2 hr after the stent placement. Tissue samples were weighed immediately after collection, digested in 1 ml of BTS-450 solution (Beckman, Fullerton, CA) at 40°C for 24 hr, and counted for 1 min in 10 ml of ready organic scintillation fluid (Beckman, Fullerton, CA). Blood samples (0.25 ml) were digested in 0.75 ml of 1:2 BTS 450/isopropanol mixture at 40°C for 24 hr, decolorized with H_2O_2, and counted in 18 ml of safety sol scintillation fluid (RPI, Mount Prospect, IL) containing 0.7% acetic acid to reduce chemoluminescence. Scintillation counts were adjusted for measured background and efficiency. The drug levels were then calculated by comparing tissue counts to the counts in a sample with a known amount of radiolabelled drug.

Explanted stents were incubated in tetrahydrofuran to dissolve the tecoflex coating and recover the residual drug. Scintillation counting of aliquots from this solution was performed to calculate the amount of drug remaining on the stent.

RESULTS

Delivery Kinetics With Stents In Situ

Figure 1 illustrates the drug levels in the media of the stented segment plotted against time. The forskolin levels reached a peak at 2 hr after stent placement and then decreased briskly with a half-life of 5.8 hr over the next 24 hr. The peak arterial wall levels of forskolin were about 780 times higher than the simultaneous blood levels. At 24 hr, the arterial wall forskolin levels were still 77-fold higher than the corresponding blood levels and 12 times higher than the known median effective concentration (EC_{50}) of forskolin (1×10^{-6} M)[10]. The etretinate concentration in the media of the stented segment increased over the 24 hours after stent placement, reaching a peak of 250 ng/mg tissue at 24 hours. These levels were 6,000-fold higher than the simultaneous blood etretinate levels. The tissue levels of etretinate decreased slowly after this with a half-life of 4.2 days. Tissue etretinate levels even at 72 hr (185 ng/mg tissue) were 4,000-fold higher than the simultaneous blood levels and 550-fold higher than the highest reported EC_{50} of the drug ($0.1–1.0 \times 10^{-6}$ M)[14]. Residual etretinate in stents removed at 72 hr was 1.4 mg (49.5% of the mean

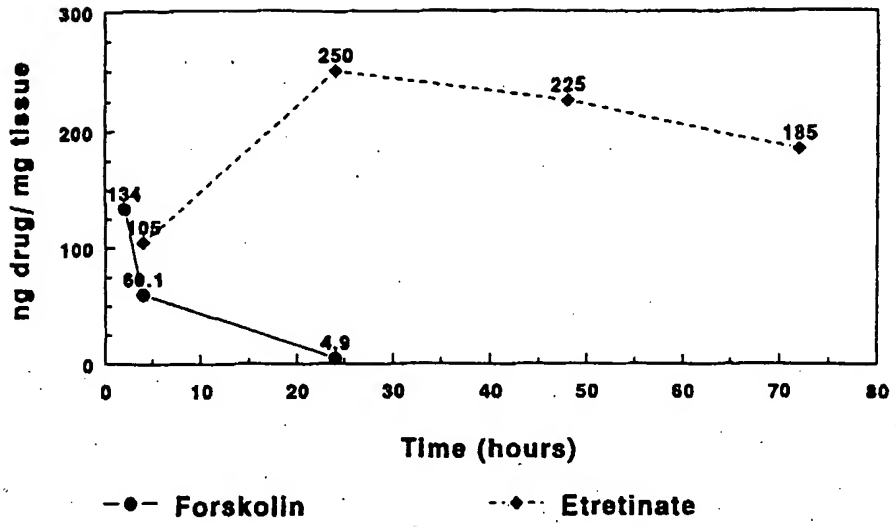

Fig. 1. A line diagram showing the changes in drug levels in the stented segment of the artery with time after the deployment of a drug-loaded stent. Etretinate levels reach a peak at 24 hr, and high levels persist up to 72 hr. Forskolin levels peak at 2 hr and then decrease rapidly.

initial etretinate load per stent), and the residual forskolin in stents removed at 24 hr was 0.08 mg (about 5% of the mean initial forskolin load per stent).

Figure 2 shows the concentrations of both the drugs in various tissues and blood. Tissue forskolin levels were measured 4 hr after placement of a drug-loaded stent. The media of the stented arterial segment has drug levels (60.1 ng/mg tissue) 460 times the levels in blood. Adventitia overlying the stented arterial segment also has high drug levels, and the proximal and distal segments of the artery have progressively decreasing drug concentrations. Figure 2 also shows the tissue distribution of etretinate 24 hr after placement of a drug-loaded stent. The media of the stented arterial segment again has the highest drug levels (250 ng/mg tissue). The dropoff of drug concentration in the adventitia of the stented arterial segment and in the proximal and distal segments of the artery is much sharper than that in the forskolin data. The drug levels in blood and the distant tissues are extremely low, and the ratio of local to systemic drug levels is very high (≈6,000).

Drug Washout Study Following Stent Removal

Figure 3 illustrates the kinetics of drug washout from the stented segment of the artery after stent removal. The forskolin levels at the time of stent removal (2 hr after stent placement) were 134 ng/mg of tissue. Within 2 hr of stent removal, the levels fell more than a 100-fold down to 1.2 ng/mg. In the next 22 hr, the levels fell further, about tenfold down to 0.12 ng/mg with a half-life of about 1.9 hr. The tissue levels of forskolin are highly dependent upon the sustained presence of the drug reservoir. On the other hand, the etretinate kinetics were different. The drug-loaded stent was removed at 72 hr, and at this time, the etretinate levels in the stented arterial segment were 74 ng/mg of tissue. Twenty-four hours later, the etretinate levels fell down to 29 ng/mg of tissue, and 96 hr after stent removal, the tissue levels were still 15 ng/mg. Etretinate gradually disappeared from the tissues after stent removal with a half-life of 1.9 days.

DISCUSSION

The study illustrates the feasibility of using polymer-coated stents for local delivery of drugs to the arterial wall. We demonstrated the ability to achieve tissue drug levels two to three orders of magnitude higher than the simultaneous blood levels and to maintain high tissue levels for 1–7 days. The study also demonstrates wide variation in the kinetics of delivery and washout rates between the two drugs tested. As such, each candidate drug for local delivery will require its own kinetics studies.

Drug Incorporation Into the Polymer

We could incorporate an average of 1.5 mg of forskolin and 2.8 mg of etretinate into the polymer-coated stent. The process of drug loading into the polymer is simple. The polymer swells up in a solution of the drug in an appropriate organic solvent mixture, absorbing drug into the swollen polymer like a sponge. The amount

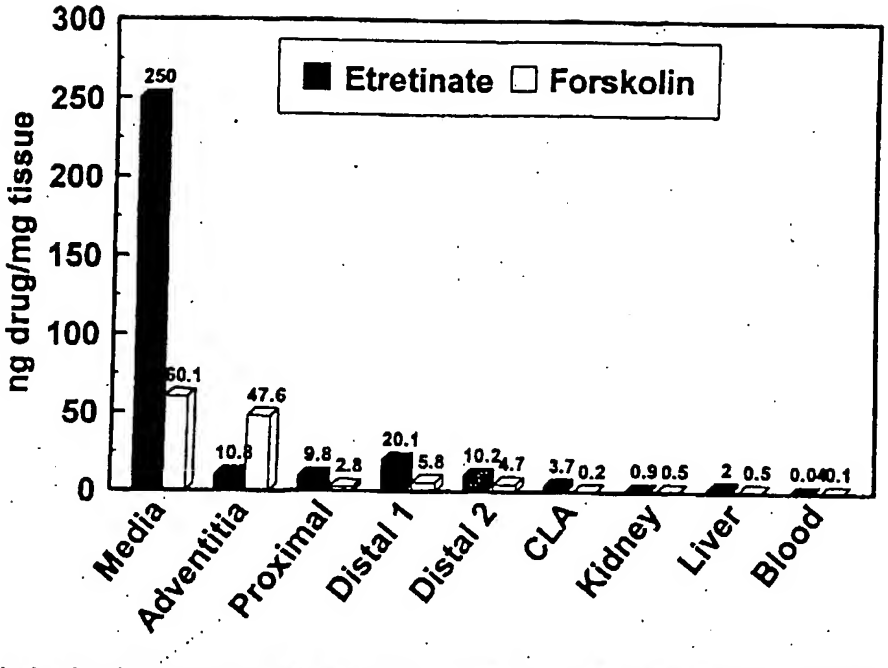

Fig. 2. A bar graph showing the comparative tissue levels of etretinate at 24 hr and forskolin at 4 hr after the placement of drug-loaded stents. Highest drug levels are achieved in the media of the stented arterial segment, and decreasing levels are observed in the arterial segment proximal or distal to the artery and the adventitia overlying the stented arterial segment. Liver, kidney, blood, and contralateral carotid artery (CLA) show very low levels of either drug.

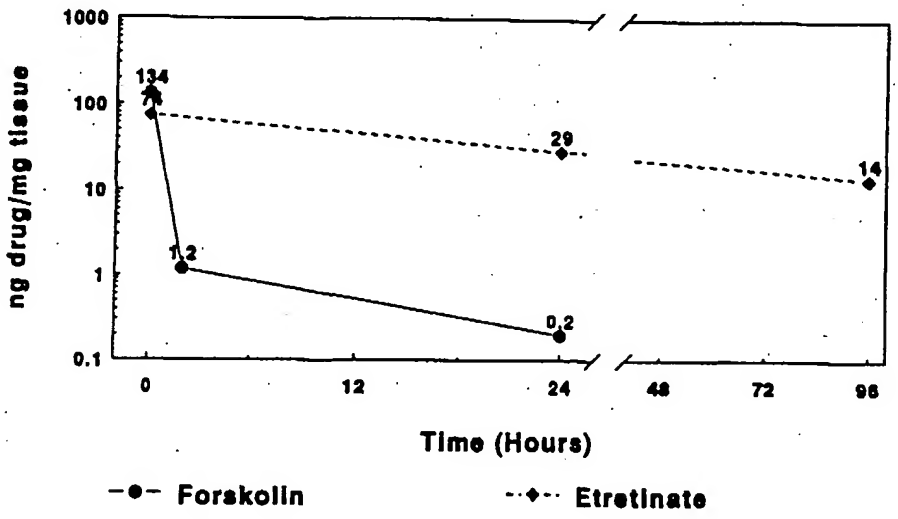

Fig. 3. A line diagram showing the drug washout from the stented segment of the artery after removal of the stent. Etretinate-loaded stents were removed at 72 hr, and forksolin-loaded stents were removed at 2 hr after stent placement. The tissue etretinate levels fell slowly with a half-life of 1.9 days after stent removal. Tissue forskolin levels rapidly fell 100-fold within 2 hr of stent removal and a further tenfold over the next 24 hr.

of drug loaded on the stent is a function of two parameters: 1) degree of polymer swelling and 2) concentration of the drug in the solution. As tecoflex swells up only in certain organic solvents, only drugs soluble in these solvents can be incorporated into tecoflex. Therefore, the hydrophobic character of the tecoflex matrix does not allow incorporation of polar water-soluble compounds. This is a limitation of the present system.

Drug Release From the Stent Coating

The drug-release kinetics from the polymer-coated stent for both forskolin and etretinate can be approximated by exponential decay functions with very different half-lives. By 24 hr post-implantation, more than 95% of the original forskolin mass was no longer detectable in the stent coating. In contrast, at 72 hr the explanted stent had about 50% of the original etretinate load. The much slower release rates of etretinate from the stent or the tissues may be related to its relative insolubility in the aqueous medium. The rate of drug release may also reflect the molecular structure of the two drugs—forskolin is a globular molecule, whereas etretinate is a linear molecule with a long side chain.

The tissue distribution of drugs (Fig. 2) shows evidence of both radial and axial diffusion of forskolin into the arterial tissue. The tissue samples from the distant organs (liver, kidney) and blood showed very low levels. The tissue distribution of etretinate follows a similar pattern. However, the target tissue (media of the stented arterial segment) concentrations were much higher and the degree of both radial and axial diffusion of the drug to the adventitia and the proximal and distal arterial segments respectively, was more limited than that of forskolin. The drug levels in the distant tissues and blood were much lower. This may reflect slower diffusion of etretinate in the aqueous medium than forskolin or presence of significant tissue binding of etretinate. With both drugs however, orders of magnitude greater concentration were reached in the target tissue than in the distant organs.

Drug Washout

The rates of drug washout from the target tissue were also different. Forskolin levels fell down 100-fold within 2 hr after stent removal and another tenfold over the next 22 hr. In contrast, the etretinate levels in the media of the stented arterial segment fell down with a half-life of about 1.9 days. The rates of decline of tissue drug levels were much faster for both drugs after stent removal than those with stent in place. This underscores the importance of continued presence of a drug reservoir for maintaining high tissue concentrations of both drugs.

Comparison With Other Systems

A number of local drug delivery systems including porous balloon catheters, double balloon catheters, hydrogel-coated balloons, and electrophoretic diffusion have been used to deliver drugs to the arterial wall [17,20]. Quantitative studies of tissue drug levels are limited. Van Lierde et al. infused ridogrel through a microporous balloon [17]. Within minutes, peak tissue levels of 167 ng/mg were reported, 34 times higher than the blood levels. By 40 min, however, the tissue drug levels were lower than the blood levels. Hong et al. [18] delivered angiopeptin to the arterial wall with a porous balloon. At 24 hr, the arterial wall angiopeptin levels were 3.2 pg/mg of tissue. The differences between these data and the tissue forskolin levels of 4.9 ng/mg ($\times$1,500) and the tissue etretinate levels of 250 ng/mg ($\times$75,000) achieved by the polymer-coated stents at 24 hr in our study are striking. The studies on local delivery of heparin via hydrogel-coated balloons [19] and of hirudin via iontophoresis [20] have shown that although high drug levels in the arterial tissues can be achieved transiently, they cannot be sustained for more than 1–3 hr. The ratio of local to systemic drug levels is an excellent index of "efficiency" of local delivery. The extremely high ratios (780 for forskolin and 6,000 for etretinate) achieved in our study suggest an efficient local drug delivery.

Limitations of the Study

1) The study provides no data on bioactivity of the drugs delivered locally. Separate studies to assess the efficacy of this local drug delivery system in the prevention of restenosis and thrombosis will be necessary. 2) Although the pattern of release of these two drugs into the tissues with the stent in place and their washout from the tissue after stent retrieval are quite different, the study has sampled the drug levels at limited time points. Hence true peak tissue drug levels might have been missed. 3) The delivery system presented is suitable only for the delivery of lipophilic drugs. We are currently working on modifications of this system for hydrophilic molecules. Finally, we need to address the question of local toxicity of such high tissue drug levels and to define appropriate parameters for the candidate drugs.

CONCLUSIONS

Our study demonstrates the feasibility of using polymer-coated coronary stents as local drug delivery devices. High drug concentrations (two to three orders of magnitude higher than the blood levels) could be achieved in the target tissue and could be sustained for 1–7 days after delivery. The kinetics of drug delivery to the tissues and the drug washout from the tissues vary between the two drugs tested and need to be studied for each candidate drug delivered by this system.

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